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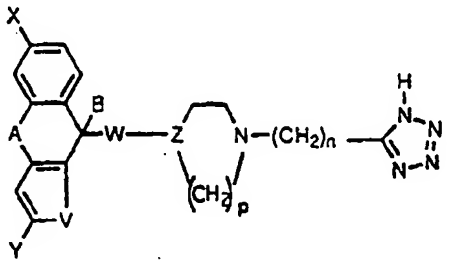
(54) Title: TETRAZOLE DERIVATIVES HAVING ANTIHISTAMINIC AND ANTIALLERGIC ACTIVITY



(1)

(57) Abstract

A tetrazole derivative of general formula (1), where A represents -CH=CH-, -CH_2-CH_2-, -CH_2O-, an oxygen atom or a sulfur atom or, in the case where A does not interconnect the adjacent aromatic rings, it represents two hydrogen atoms each bonded to the adjacent aromatic ring; V represents -CH=CH- or a sulfur atom; X and Y each independently represents an alkoxy group, a halogen atom or a hydrogen atom; (a) W represents a bond, Z represents a carbon atom or methine, and B either forms a bond together with Z or represents a hydroxyl group, or (b) W, Z and B represent a bond, a nitrogen atom and a hydrogen atom, respectively, or (c) W, Z and B represent an oxygen atom, methine and a hydrogen atom, respectively; p represents an integer of 2 or 3; and n represents an integer of 1-6 or a pharmacologically acceptable salt thereof, or an antihistamine, an anti-allergic agent or an asthma treating agent containing the same.

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DESCRIPTION

TETRAZOLE DERIVATIVES HAVING ANTIHISTAMINIC AND ANTIALLERGIC ACTIVITY

BACKGROUND OF THE INVENTION:

This invention relates to novel tetrazole derivatives or salts thereof, as well as antihistamines, antiallergic agents and asthma treating agents that contain the novel tetrazole derivatives or salts thereof and which exhibit satisfactory antihistaminic and antiallergic actions while causing less central nervous system depressing effects. The compounds of the invention are also effective in the treatment of rhinitis, nephritis, atopic dermatitis and psoriasis.

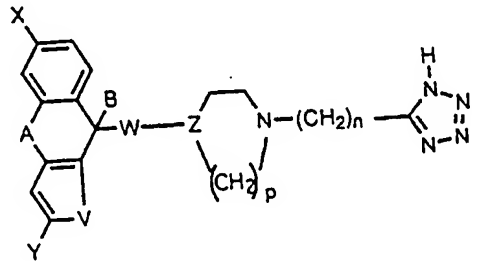
A number of benzhydryl derivatives have heretofore been synthesized and their various pharmacological actions including antiallergic action are under review. European Patent No. 82-870006 and Japanese Patent Public Disclosure (Kokai) No. Hei 3-246287 teach certain kinds of carboxylic acid derivatives, and WO 93/02062 teaches certain kinds of tetrazole derivatives. Japanese Patent Public Disclosure (Kokai) Nos. Hei 4-234359 and 4-234387 teach piperazine derivatives. However, these compounds have been unsatisfactory in that their efficacy is insufficient or that they cause central nervous system depressing effects such as sleepiness and sedation. It should also be mentioned that the prior art compounds are capable of suppressing the early-phase reaction in asthma but their ability to suppress the late-phase reaction has been insufficient. Under the circumstances, steroids are currently used in the treatment of asthma of the late-phase reaction type but steroids have their own problems, namely, those of side effects. Conventional antihistamines also have had defects, one of which is that they have anticholinergic actions causing side effects such as thirst and mydriasis. With a view to solving these problems, various studies have so far been conducted but the results have not been completely satisfactory.

SUMMARY OF THE INVENTION:

An object, therefore, of the present invention is to provide compounds that exhibit more satisfactory antiallergic and antihistaminic actions, that are effective against both early- and late-phase reaction in asthma and which yet are highly safe in use.

Under the circumstances described above in connection with the prior art, the present inventors synthesized many tetrazole derivatives and reviewed their antihistaminic, antiallergic and central nervous system depressing actions. Surprisingly enough, they found that tetrazole derivatives of the general formula (1) to be defined below or salts thereof exhibited satisfactory antihistaminic and antiallergic actions and that, in addition, those derivatives or salts thereof were as effective as steroids in suppressing the late-phase reaction in asthma, while causing only weak central nervous system depressing effects. The present invention has been accomplished on the basis of this finding.

The present invention, in its first aspect, provides tetrazole derivatives of the general formula(1):



(where A represents -CH=CH-, $-CH_2-CH_2-$, $-CH_2O-$, and oxygen atom or a sulfur atom or in the case where A does not interconnect the adjacent aromatic rings, it represents two hydrogen atoms each bonded to the adjacent aromatic ring; V represents -CH=CH- or a sulfur atom; X and Y each independently represents an alkoxy group, a halogen atom or a hydrogen atom; (a) W represents a bond, Z represents a carbon atom or methine, and B either forms a bond together

with Z or represents a hydroxyl group, or (b) W, Z and B represent a bond, a nitrogen atom and a hydrogen atom, respectively, or (c) W, Z and B represent an oxygen atom, methine and a hydrogen atom, respectively; p represents an integer of 2 or 3; and n represents an integer of 1 - 6) or pharmacologically acceptable salts thereof.

In its second aspect, the invention provides an antihistamine, an antiallergic agent and an asthma treating agent that contain those tetrazole derivatives or pharmacologically acceptable salts thereof as effective ingredients.

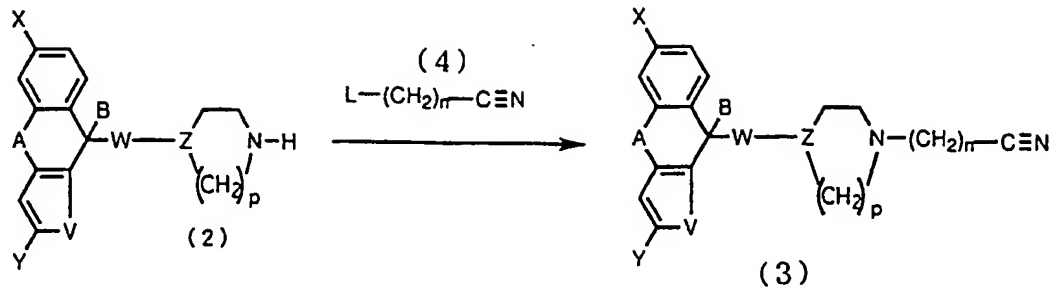
DETAILED DESCRIPTION OF THE INVENTION:

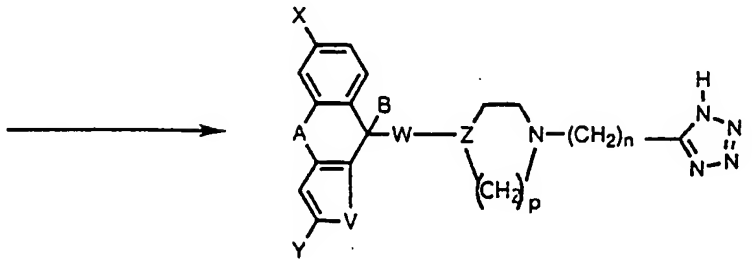
Some of the compounds of the present invention have optical isomers and in that case the invention encompasses all applicable isomers.

Salts of the compounds of the invention are any medicinally acceptable salts that are exemplified by, but in no way limited to, addition salts of acids including hydrochloric acid, nitric acid, sulfuric acid, maleic acid, fumaric acid, oxalic acid, citric acid, hydrobromic acid, tartaric acid, succinic acid, sulfamic acid, mandelic acid, malonic acid and phosphoric acid, as well as basic salts including sodium salts, potassium salts, lithium salts, calcium salts and zinc salts.

Compounds (1) of the invention may be produced by the following reaction scheme 1):

1)





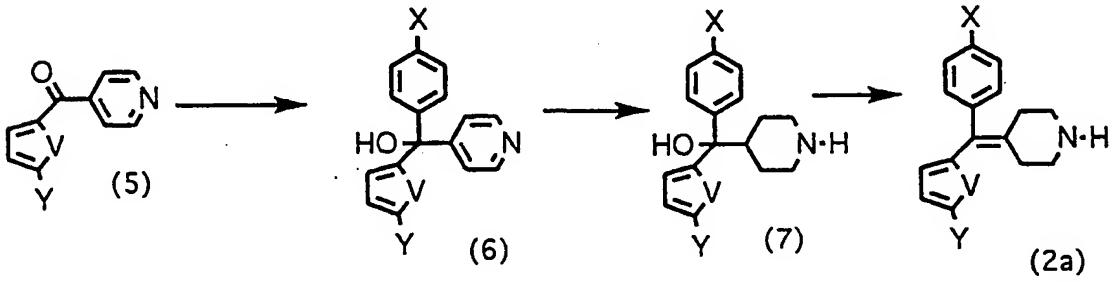
(where V, W, X, Y, Z, p, n, A and B have the same meanings as defined above, and L represents a halogen atom).

In this step, the compounds represented by the general formula (2) are reacted with compounds of the general formula (4) in the presence of bases to prepare compounds represented by the general formula (3). The reaction is preferably carried out in inert solvents. Exemplary solvents include:water; esters such as methyl acetate and ethyl acetate; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; halogenated hydrocarbons such as dichloromethane and chloroform; aromatic hydrocarbons such as benzene, toluene and xylene; others such as acetonitrile, dimethyl sulfoxide and dimethylformamide. These solvents may be used either independently or in combination. The reaction temperature varies with the starting materials to be used but the range from 0 to 200°C may typically be adopted. Base catalysts are generally effective for but by no means indispensable to the progress of the

reaction. Preferred bases include potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, triethylamine, pyridine and tributylammonium hydroxide. Compounds of the general formula (3) may further be reacted with trialkyltin azide or trialkylsilye azide; alternatively, the compounds may be reacted with metal salts of hydrogen azide such as sodium azide or potassium azide in the presence of ammonium salts. This reaction is preferably carried out in inert solvents such as xylene, toluene, benzene, tetrahydrofuran, dioxane, dimethylformamide and N-methylpyrrolidone, which may be used either independently or in combination. The reaction temperature varies with the starting materials to be used but the range from 0 to 200°C may typically be adopted.

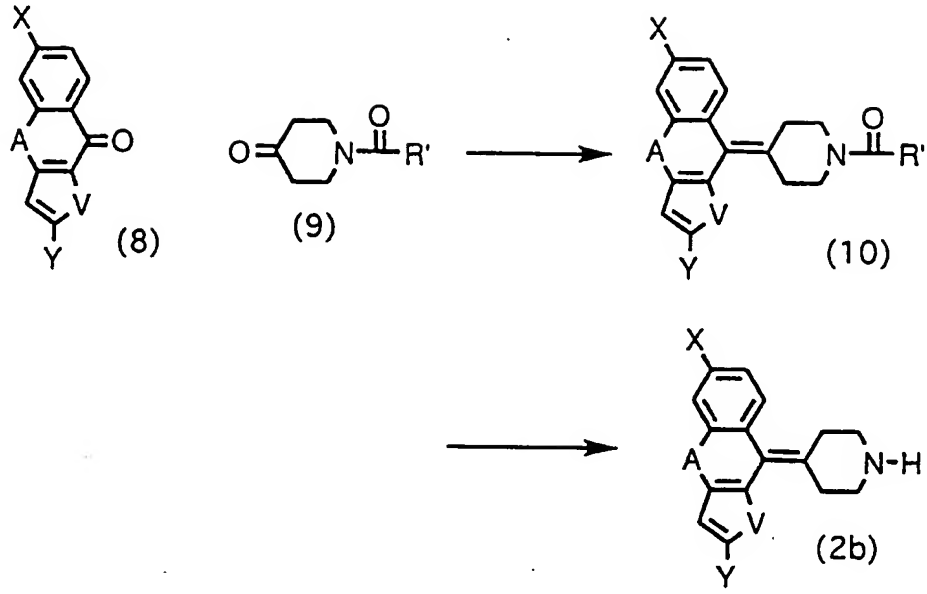
Compounds represented by the structural formula (2) are either known or synthesizable by reaction in accordance with one of the following schemes 2), 3) or 4):

2)



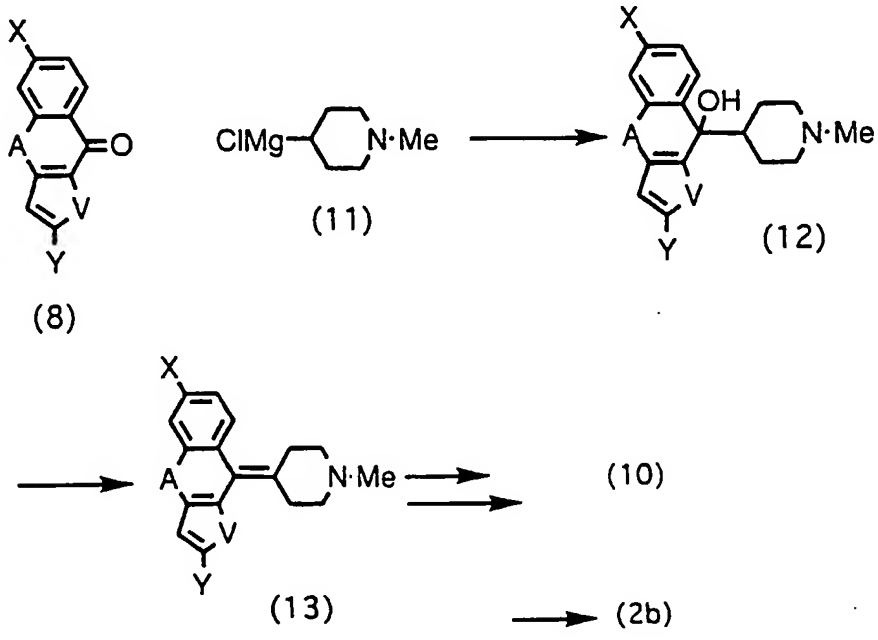
Conversion from (5) to (6) can be accomplished by causing a substituted phenyl magnesium halide or substituted phenyl lithium to act on (5). Conversion from (6) to (7) can be accomplished by causing a catalyst (e.g. platinum oxide, palladium on carbon, or palladium) to act in hydrogen at either atmospheric or superatmospheric pressure. Conversion from (7) to (2a) can readily be accomplished either under acidic conditions (e.g. acetic acid-sulfuric acid) or under ordinary dehydrative reactive conditions (e.g. toluenesulfonic acid-benzene).

3)



Conversion from (9) to (10) can be accomplished by using titanium in a lower oxidation state. Any inert solvents may be used and preferred examples are ethereal solvents such as dioxane, tetrahydrofuran, dimethoxyethane and ether.

4)



Conversion from (8) to (12) can be accomplished by known methods. Conversion from (12) to (13) can readily be accomplished either under acidic conditions (e.g. acetic acid-sulfuric acid) or under ordinary dehydrative reaction conditions (e.g. toluenesulfonic acid-benzene). Conversion from (13) to (2b) can be accomplished by first causing an alkyl chloroformate to act on (13) to form a carbamate and then hydrolyzing it with an alkali.

Specific examples of the compounds of the present invention are listed below.

Compound 1:
4-Dibenzo[a,d]cyclohepten-5-ylidene-1-[3-(1H-tetrazole-5-yl)propyl]piperidine

Compound 2:
4-Dibenzo[a,d]cyclohepten-5-ylidene-1-(1H-tetrazol-5-ylmethyl)piperidine

Compound 3:
4-Dibenzo[a,d]cyclohepten-5-ylidene-1-[4-(1H-tetrazol-5-yl)-butyl]piperidine

Compound 4:
4-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 5:
4-(6H-Dibenzo[b,e]oxepin-11-ylidene)-1-[3-(1H-tetrazol-5-yl)-propyl]piperidine

Compound 6:
4-[Bis(4-fluorophenyl)methylene]-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 7:
4-(phenyl-2-thienylmethylene)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 8:
4-Benzhydrylylidene-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 9:
4-Benzhydrylylidene-1-[5-(1H-tetrazol-5-yl)pentyl]piperidine

Compound 10:
α,α-Diphenyl-N-[3-(1H-tetrazol-5-yl)propyl]piperidin-4-ylmethanol

Compound 11:
4-[Bis(4-methoxyphenyl)methylene]-1-[4-(1H-tetrazol-5-yl)butyl]piperidine

Compound 12:
4-Dibenzo[a,d]cyclohepten-5-ylidene-1-[5-(1H-tetrazol-5-yl)pentyl]piperidine

Compound 13:
4-Xanthen-9-ylidene-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 14:
4-Thioxanthen-9-ylidene-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 15:
1-Benzhydryl-4-[3-(1H-tetrazol-5-yl)propyl]piperazine

Compound 16:
1-Benzhydryl-4-[3-(1H-tetrazol-5-yl)propyl]-[1,4]diazepan

Compound 17:
1-Benzhydryl-4-(1H-tetrazol-5-ylmethyl)piperazine

Compound 18:
1-Benzhydryl-4-[4-(1H-tetrazol-5-yl)butyl]piperazine

Compound 19:
1-[(4-chlorophenyl)phenylmethyl]-4-[3-(1H-tetrazol-5-yl)propyl]piperazine

Compound 20:
1-[Bis(4-fluorophenyl)methyl]-4-[3-(1H-tetrazol-5-yl)propyl]piperazine

Compound 21:
4-Benzhydryloxy-1-[3-(1H-tetrazol-5-yl)propyl]-piperidine

Compound 22:
4-[(4-chlorophenyl)phenylmethoxy]-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 23:
4-[Bis(4-fluorophenyl)methoxy]-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 24:
4-[(4-chlorophenyl)phenylmethoxy]-1-[4-(1H-tetrazol-5-yl)butyl]piperidine

Compound 25:
4-(Phenyl-p-chlorophenylmethylene)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 26:
4-(10,11-Dihydrodibenzo[a,d]cycloheptan-5-yl)-1-[3-(1H-tetrazol-5-yl)propyl]piperazine

Compound 27:
4-(10,11-Dihydrodibenzo[a,d]cycloheptan-5-yl)-1-[4-(1H-tetrazol-5-yl)butyl]piperazine

Compound 28:
4-(6H-Dibenzo[b,e]oxepin-11-yl)-1-[3-(1H-tetrazol-5-yl)propyl]piperazine

Compound 29:
4-(Dibenzo[a,d]cyclohepten-5-yl)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

Compound 30:
4-(Dibenzo[a,d]cyclohepten-5-yl)-1-[4-(1H-tetrazol-5-yl)butyl]piperidine

Compound 31:
4-(6H-Dibenzo[b,e]oxepin-11-yl)-1-[4-(1H-tetrazol-5-yl)butyl]piperazine

Compound 32:
4-[(4-Chlorophenyl)phenylmethylene]-1-[4-(1H-tetrazol-5-yl)butyl]piperidine

Compound 33:
4-[(4-Chlorophenyl)phenylmethylene]-1-[3-(1H-tetrazol-5-yl)propyl]piperidine

The compounds of the invention or pharmacologically acceptable salts thereof may be formulated for peroral or parenteral administration by mixing them with adjuvants that are acceptable in pharmaceutical formulation procedures.

Solid pharmaceutical formulations for peroral administration include tablets, powders, granules and capsules and these can be produced by combining the compound (1) of the invention with suitable additives such as excipients (e.g. lactose, mannitol, corn starch and crystalline cellulose), binders (e.g. cellulose derivatives, gum arabic and gelatin), disintegrators

(e.g. carboxymethyl cellulose calcium), and lubricants (e.g. talc and magnesium stearate). If desired, these solid preparations may be formulated as enteric drugs by coating with bases such as hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, cellulose acetate phthalate and methacrylate copolymer. Liquids for peroral administration may be exemplified by emulsions, solutions, suspensions, syrups and elixirs and these can be produced by combining the compound (1) of the invention with commonly employed inert diluents such as purified water and ethanol. In addition to inert diluents, the resulting compositions may contain adjuvants (e.g. wetting agents or suspending agents), sweeteners, flavoring agents, fragrances and antiseptics. Other applicable dosage forms are aerosols that can be produced by known methods.

Pharmaceutical preparations for parenteral administration include liquids for injection and they can be produced by combining the compound (1) of the invention with water, ethanol, glycerin, common surfactants, etc. Other parenteral dosage forms include inhalers, liquids for external application, eye drops, nasal solutions and liniments such as ointments.

The dosage of the compound (1) of the invention depends on various factors including age, body weight, the severity of the disease, the efficacy in treatment, the method of administration and the period of administration. Typically, the compounds are administered perorally one to three times a day at doses of 1 - 500 mg, preferably 5 - 50 mg. Alternatively, they may be administered parenterally one to several times a day at doses of 0.1 - 500 mg.

The pharmacological actions of representative examples of the compound (1) and salts thereof are described below.

Test 1: Histamine H_1-receptor antagonism in vitro

Trachea were removed from Male Hartley guinea-pigs (300 - 600g) and cut into strips. The tissues were suspended in 20-ml jacketed organ baths containing Tyrode physiological solution, aerated with 95% O_2: 5% CO_2 and maintained at 37°C. Changes in isometric tension were measured with a force-displacement transducer and recorded on a polygraph. The preparations were placed under 1 g of passive tension and allowed to equilibrate for 30 - 60 min. The efficacy of test compounds on histamine(10^{-5} M)-induced constriction was calculated and expressed as Inhibitory concentration of 50% (IC_{50}). The data obtained are shown in Table 1.

Cetirizine (see Japanese Patent Public Disclosure No. Sho 57-149282) used as a control had an IC_{50} of 2.40 μM.

Table 1

Compounds	IC_{50} (μM)
compound 1	0.08
compound 5	0.04
compound 15	0.07
compound 20	0.08
compound 21	0.01
oxatomide	0.13
diphenhydramin	0.3
ketotifene	0.08

Test 2: Antiallergic effect(s)

Passive cutaneous anaphylaxis (PCA) in rats: Male SD rats were sensitized intradermally on their shaved backs with 0.1 ml of appropriately diluted homologous anti-serum containing anti-dinitrophenyl conjugated Ascaris (DNP-As). Forty eight hours later, the rats were challenged with 1 ml of saline containing 300 μg of DNP-As and 5 μg of Evans blue. Thirty minutes after the challenge, the rats were killed, and the skin of the back was removed. The severity of PCA was assessed by measuring the dye exudate into the

skin according to the method of Harada (Japanese Journal of Allergology, 15,1). Test compounds were suspended in 0.5% methyl cellulose in saline and administered (p.o.) before 60 min. of the challenge. The data of inhibiting PCA was expressed by the amount of dye exudate on the site (Table 2).

Table 2

Compounds	Inhibition(%)
compound 1	99
compound 7	99
compound 19	70
compound 20	81
compound 21	80
compound 22	79
compound 25	71
ketotifene	99
oxatomide	53

Test 3: Acute toxicity

Groups of 4 - 5 wk-old ICR mice were used, each group consisting of 5 animals.

Each compound was suspended in 0.5% methyl cellulose in saline and administered 100 mg/Kg (i.p.). Observation was made for 7 days. No animals administered the test compounds were dead at this dosage, but diphenhydramin was lethal at 100 mg/Kg.

Test 4: Effect on Pentobarbital Induced Sleep

Groups of 4 or 5 wk-old ICR mice were used, each group consisting of 10 animals.

Each of the test compounds was suspended in 0.5% methyl cellulose solution and administered orally at a dose of 25 mg/Kg. One hour later, pentobarbital was injected intraperitoneally at a dose of 40 mg/Kg to induce coma. The moment the animal lost the righting reflex to lie on the back was regarded the start of coma and the

moment it recovered the righting reflex was regarded as the end of coma.

Terfenadine was used as a control compound, which is a known antiallergic agent that is not a strong sleep inducer. The data obtained are shown in Table 3 as the percent increase in sleep time compared to the negative control group (given no compounds).

Table 3

Compounds	Increase in Sleep Time (%)
Terfenadine	+ 44
Compound 3	- 9
Compound 6	+ 4
Compound 20	- 31

Thus, the invention compounds were verified to have a smaller central nervous system depressing action.

Test 5: Inhibitory effects on leukocytes recruited into Guinea-pig broncoalveolar lavage fluid

This experiment was conducted according to the methods described in America Review of Respiratory Disease, 1990,142,680-685. Male Hartley Guinea-pig (5 weeks old) was passively sensitized with injection of 0.25 ml of anti-ovalbumin (raised in rabbit). Forty eight hours later the animals were treated with mepyramin (an H_1-receptor antagonist, i.p.) in order to avoid anaphylactic death, then applied to plastic exposure-chamber connected with ultrasonic nebulizer, where 0.25% ovalbumin in saline was inhalated for 10 min. Twenty four hours later, the treated guinea-pigs were administered overdose of pentobarbital, and lung were lavaged with 25 ml of phosphate buffered saline (pH 7.4) through a polyethylene tube introduced through tracheostomy. Total cells in the lavage fluid were counted by Coulter Counter, and differential cell counts were determined from cytospun preparations and stained by May-Gruenwald Giemza stain.

Cells were identified as macrophage, neutrophils, eosinophils and lymphocytes by standard morphology, and absolute number of each cell type were calculated. Each compound suspended in 0.5% methyl cellulose containing 0.05% Tween 80 was administered (30 mg/Kg, p.o.) two times (1 hour before and 6 hours after ovalbumin-challenge).

Inhibition of recruitment of leukocytes into lavage fluid were expressed;

Inhibition (%)

$$\left[1- \frac{\text{(cells in treated animals)} - \text{(cells in non-challenged animals)}}{\text{(cells in non-treated animals)} - \text{(cells in non-challenged animals)}}\right] \times 100$$

In these series of experiments, the compounds tested showed the efficacy to inhibiting the recruitment of leukocytes into bronchoalveolar fluid; showing the ability to employ to allergic late phase reactions. In contrast, oxatomide, ketotifene and diphenyldramin showed no inhibitory effects on this experiment. Cetirizine had weak effects as noted below.

Table 4

Inhibition (%)

Compounds	Eosinophils	Neutrophils	Monocyte
compound 22	69	46	14
compound 19	53	67	63
compound 21	60	20	25
compound 26	29	73	84
compound 6	28	70	79
compound 20	52	67	0
cetirizine	15	10	8

Test 6: Anti-Anaphylactic Bronchoconstriction

Bronchoconstriction was measured by the overflow technique of Konzett and Roessler. Male guinea-pigs (5 weeks, 300-350 g) were passively sensitized by an injection with anti-ovalbumin rabbit serum (0.1 ml/animal, i.v.). Two days later, the animals were anesthetized with urethane (1.5 g/Kg; i.p.). The trachea was canulated for artificial ventilation. The right jagular vein was canulated for administration of test compound and antigen. Spontaneous respiration was abolished by gallamine triethiodide (5 mg/Kg). The animals were artificially ventilated at 60 strokes per minute (stroke volume of 10 ml/Kg). Bronchoconstriction was measured as the volume of inspiration overflow using a Ugo Bassile 7020 bronchospasm transducer. The compounds (1 mg/Kg) were administered intravenously 15 min. before antigen challenge. In control group, vehicle alone was administered instead of the compounds.

The guinea-pigs were challenged with intravenous administration of ovalbumin (0.1 mg/Kg), then changes in the overflow volume were recorded for 30 min. Bronchoconstriction was represented as, (1) the peak height and (2) the area under the curve (AUC) of each trace. Percent inhibition of bronchoconstriction is then calculated in terms of the peak height or the AUC as follows;

$$\frac{\text{Increase in V (control group)} - \text{Increase in V (test group)}}{\text{Increase in V (control group)}} \times 100$$

where V means "Bronchoconstriction represented as peak hight or AUC"

Table 5

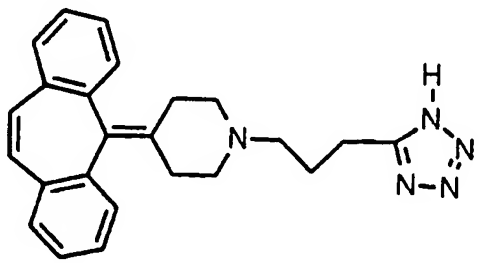
	Inhibition (peak height, %)	Inhibition (AUC, %)
compound 22	35	52
compound 21	53	59
centilizine	20	19
Example 62 (WO 93/02062)	18	16

The results of Tests 1 - 6 show that the compounds of the invention had satisfactory antihistaminic and antiallergic effects and proved to be significantly effective against both late- and early-phase reactions in asthma. It should particularly be noted that compounds 21 and 22 at the most preferred since they are potent suppressors of not only bronchoconstriction which occurs at the early phase of asthma but also the recruitment of leukocytes into bronchoalveolar fluid which occurs at the late stage of asthma. In view of these pharmacological effects they have, the compounds of the invention are also useful for the treatment of rhinitis, nephritis, atopic dermatitis and psoriasis.

The following examples are provided for the purpose of further illustrating the present invention but are in no way to be taken as limiting.

Example 1

4-Dibenzo[a,d]cyclohepten-5-ylidene-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



4-Dibenzo[a,d]cyclohepten-5-ylidenepiperidine (5 g, 18.3 mmol), bromobutyronitrile (2.7 g, 18.3 mmol) and potassium carbonate (10 g) were suspended in DMF and stirred at 100°C for 3 h. The reaction solution was poured into water, subjected to extraction with ether, dried and concentrated under vacuum to yield an oil of 4-(4-di-benzo[a,d]cyclohepten-5-ylidenepiperidin-1-yl)butyronitrile.

IR(nujol): cm^{-1}: 2250, 1490, 1435, 1135

Without further purification, sodium azide (5.9 g, 0.92 mmol) and ammonium chloride (4.9 g, 0.92 mmol) were added to the compound and the mixture was stirred overnight at 110°C. The stirred reaction mixture was poured into water, adjusted to a pH of 6, subjected to extraction with chloroform, dried and concentrated under vacuum to an approximate volume of 30 ml. The concentrate was left to stand and the precipitating crystals were collected to yield the titled compound as a powder.

m.p. (with decomposition): 134 - 139°C

Elemental analysis for $C_{24}H_{25}N_5 \cdot 2H_2O$

	C	H	N
Cal'd	68.71	6.97	16.69
Found	69.08	7.21	16.85

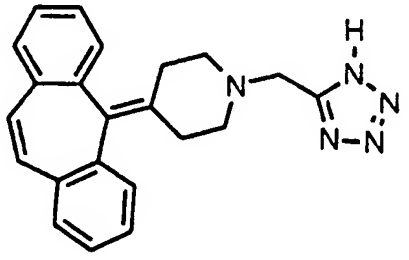
MS(m/z): 384 (M+H), (SIMS)

IR(nujol): cm^{-1}: 1300, 1160, 1080, 990, 960, 950, 880

NMR(DMSO-d_6) δppm: 7.37: (4H,m), 7.28 (2H,d,J=7.3), 6.96 (2H,s), 2,85 (2H,t,J=7.2), 2.66 (2H,t,J=7.2), 2.46 (2H,m), 2,27 (4H,m), 2.01 (2H,m), 1.86 (2H,m)

Example 2

4-Dibenzo[a,d]cyclohepten-5-ylidene-1(1H-tetrazol-5-ylmethyl)piperidine:



4-Dibenzo[a,d]cyclohepten-5-ylidenepiperidine (3.8 g, 14 mmol), bromoacetonitrile (1.68 g, 14 mmol) and potassium carbonate (5.5 g) were suspended in DMF and stirred at 100 °C for 3 h. The reaction solution was poured into water, subjected to extraction with ether, dried and concentrated under vacuum to yield an oil of 4-(4-dibenzo[a,d]cyclohepten-5-ylidenepiperidin-1-yl)-acetonitrile. Without further refining, sodium azide (2.99 g, 40.2 mmol) and triethylammonium chloride (2,77 g, 20.1 mmol) were added to the compound and the mixture was stirred in methylpyrrolidone (50 ml) for 3 h at 150 °C. The stirred reaction mixture was poured into water and adjusted to a pH of 6, subjected to extraction with chloroform, dried and concentrated under vacuum. The residue was subjected to silica gel chromatography and crystallized from ethyl acetate, yielding the titled compound in an amount of 3.19 g (62%).

m.p.: 231 - 233 °C

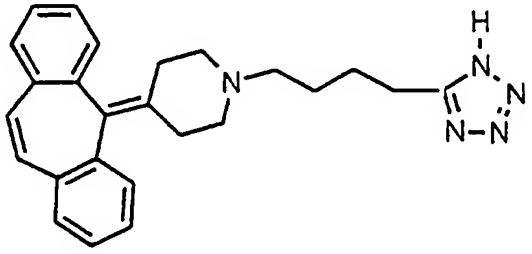
MS(m/z): 356(M+H), 277, 185

IR(nujol): cm^{-1}: 1630, 1305, 1270, 1160, 1025, 950

Similar procedures were taken in Examples 3 to 14 to synthesize the titled compounds.

Example 3

4-Dibenzo[a,d]cyclohepten-5-ylidene-1-[4-(1H-tetrazol-5-yl)butyl]piperidine:



Foam

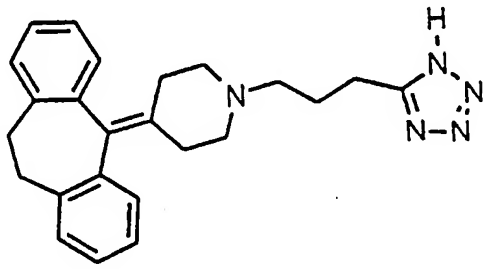
MS(m/z): 398(M+H), 286, 185(SIMS)

IR(nujol): cm^{-1}: 1650, 1550, 1300, 1250, 950, 800, 760

NMR(DMSO-d_6) δppm: 7.49 (4H,m), 7.40 (2H,m), 7.31 (2H,d,J=8.3), 7.08 (2H,s), 2.95 (2H,t,J=7.2), 2.71 (2H,t,J=7.2), 2.49 (2H,t,J=6.9), 2.37 (4H,m), 2.12 (2H,m), 1.77 (2H,m), 1.58 (2H,m)

Example 4

4-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



Foam

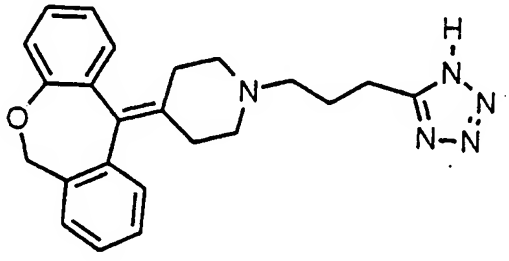
MS(m/z): 386 (M+H), (SIMS)

IR(nujol): cm^{-1}: 1640, 1295, 950, 750

NMR(DMSO-d_6) δppm: 7.0 - 7.4 (8H,m), 4.03 (1H,s), 3,89 (2H,m), 2,85 (2H,t,J=7), 2.72 (2H,m), 2.44 (4H,m), 1,84 (2H,quintet,J=7)

Example 5

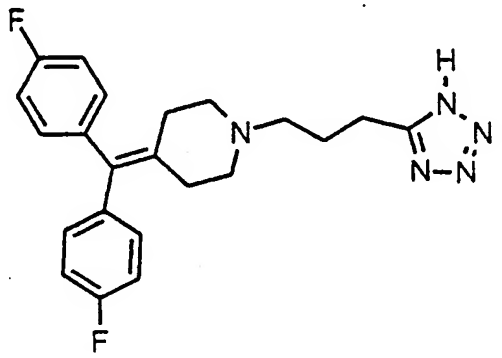
4-(6H-Dibenzo[b,e]oxepin-11-ylidene)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



m.p. (with decomposition): 192 - 196°C
MS(m/z): 388 (M+H), 290 (SIMS)
IR(nujol): cm^{-1}: 2700, 1550, 1290, 1220, 760
NMR(DMSO-d_6) δppm: 7.50 (1H,d,J=6), 7.35 (2H,m), 7.0-7.3 (3H,m), 6,84 (1H,t,J=7), 6.73 (1H,d,J=7), 3.1-3.6 (6H,m) 2.99 (4H,m), 2.88 (2H,m), 2.79 (2H,m), 2.13 (2H, quintet, J=7)

Example 6

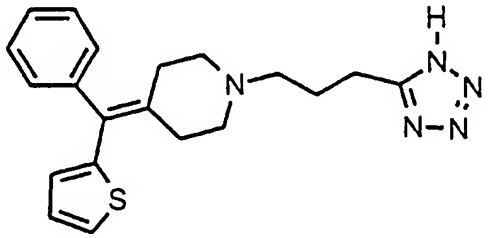
4-[Bis(4-fluorophenyl)methylene]-1-[3-(1H-tetrazol-5-yl)propyl)piperidine:



Colorless powder
m.p.: 185 - 187°C (from ethyl acetate)
MS(m/z): 396(M+H). 298, 106 (SIMS)
IR(nujol): cm^{-1}: 1600, 1500, 1450, 1410, 1220, 1160, 840
NMR(DMSO-d_6) δppm: 7.21 (8H,m), 2.96 (2H,t,J=7.3), 2.68 (4H,t,J=5.3), 2.59 (4H,t,J=2.0), 2.35 (2H,t,J=5.3), 1.98 (2H,m)

Example 7

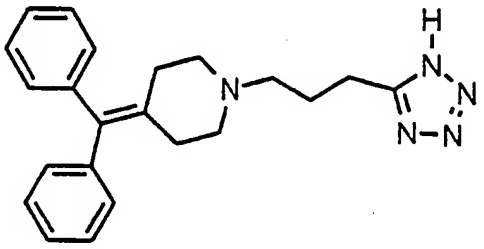
4-(Phenyl-2-thienylmethylene)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



m.p.: 215 - 219 °C
MS(m/z): 366(M+H), 268(SIMS)
IR(nujol): cm^{-1}: 1405, 1340, 1080, 970, 830, 705
NMR(DMSO-d_6) δppm: 7.57 (1H,dd,J=1.0,5.3), 7.43 (3H,m), 7.26 (2H,m), 7.12 (1H,dd,J=4.9,3.3), 6.97 (1H,m), 3.00 (2H,t,J=7.2), 2.62 (8H,m), 2.35 (2H,t,J=5.3), 2.00 (2H,m)

Example 8

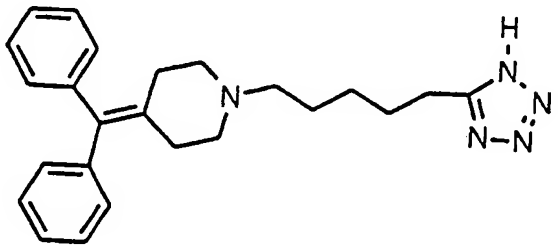
4-Benzhydrylylidene-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



Colorless powder
m.p.: 223 - 226 °C (from ethyl acetate)
MS(m/z): 360(M+H), 262, (SIMS)
IR(nujol): cm^{-1}: 1600, 1500, 1450, 1410, 1220, 1160, 840
NMR(DMSO-d_6) δppm: 7.21 (10H,m), 2.96 (2H,t,J=7.3), 2.68(4H,t,J=5.3), 2.59 (4H,t,J=2.0), 2.35 (2H,t,J=5.3), 1.98 (2H,m)

Example 9

4-Benzhydrylylidene-1-[5-(1H-tetrazol-5-yl)pentyl]piperidine:



Foam

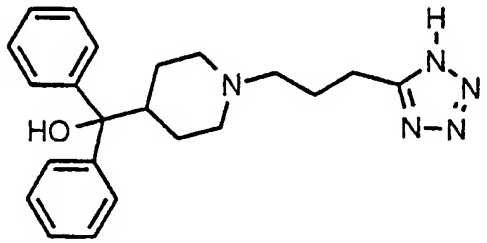
MS(m/z): 388(M+H), (SIMS)

IR(nujol): cm^{-1}: 1600, 1500, 1450, 1410, 1220, 1160, 840

NMR(DMSO-d_6) δppm: 7.2-7.6 (10H,m), 3.01 (2H,t,J=7), 2,81 (4H,t,J=7), 2.64(4H,m), 2.48 (2H,m), 1.86 (2H,quintet,J=7), 1.66 (2H,quintet,J=7), 1.48 (2H,quintet,J=7)

Example 10

α,α-Diphenyl-N-[3-(1H-tetrazol-5-yl)propyl]piperidin-4-yl-methanol:



m.p.(with decomposition) ≧ 250°C

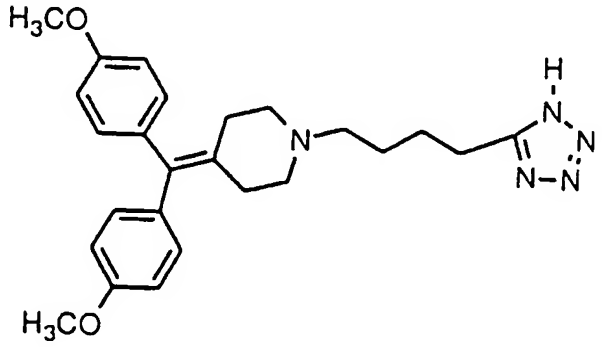
MS(m/z): 378(M+H), 133, 105

IR(nujol): cm^{-1}: 1660, 1170, 1100, 1060

NMR(DMSO-d_6) δppm: 7.51 (4H,d,J=7.6), 7.27 (4H,t,J=6.9), 7.14 (2H,dd,J=7.6,6.9), 3.20 (2H,d,J=11.2), 2.79 (4H,m), 2.50 (8H,m), 1.92 (2H,m), 1.63 (1H,m), 1.35 (2H,d,J=12.6)

Example 11

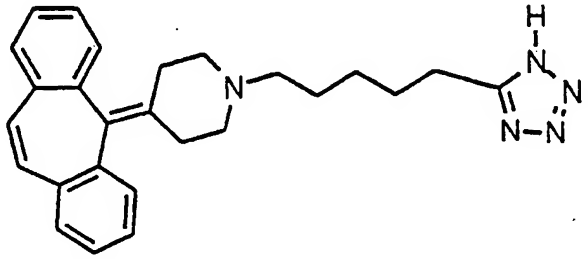
4-[Bis(4-methoxyphenyl)methylene]-1-[4-(1H-tetrazol-5-yl)butyl]-piperidine:



m.p.: 120 - 123°C
MS(m/z): 434(M+H), 322, 121
NMR(DMSO-d_6) δppm: 6.95 (4H,d,J=8.6), 6.85 (4H,d,J=8.6), 3.72 (6H,s), 2.84 (2H,t,J=7.2), 2.55 (4H,brs), 2.50 (4H,brs), 2.30 (2.50,m), 1.69 (2H,m), 1.50 (2H,m)

Example 12

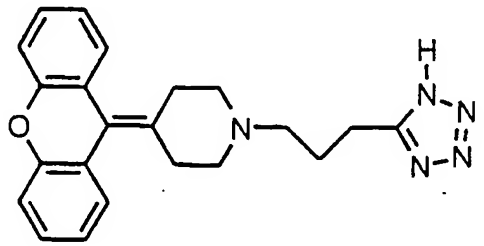
4-Dibenzo[a,d]cyclohepten-5-ylidene-1-[5-(1H-tetrazol-5-yl)pentyl]piperidine:



Colorless powder
MS(m/z): 412(M+H), (SIMS)
IR(nujol): cm^{-1}: 1650, 1550, 1300, 1250, 950, 800, 760
NMR(DMSO-d_6) δppm: 7.51 (4H,m), 7.43 (2H,m), 7.33 (2H,d,J=8.3), 7.10 (2H,s), 2.94 (2H,t,J=7.2),2.75 (2H,t,J=7.2), 2.40 (4H,t,J=6.9), 2.16 (4H,m), 1.80 (2H,m), 1.59 (2H,m), 1.44 (2H,m)

Example 13

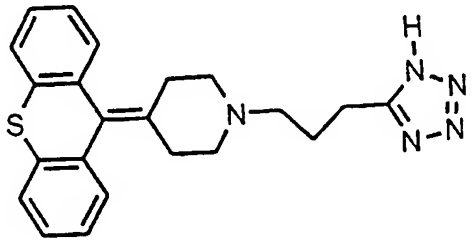
4-Xanthen-9-ylidene-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



m.p. ≧ 250 °C (from ethyl acetate)
MS(m/z): 374(M+H), (SIMS)
IR(nujol): cm^{-1}: 2450, 1590, 1550, 1250, 1200, 1150, 1100, 1060, 1050,
NMR(DMSO-d_6) δppm: 7.2-7.7 (8H,m), 2.8-3.6 (12H,m), 2.25 (2H,quintet,J=7)

Example 14

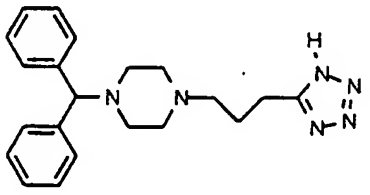
4-Thioxanthen-9-ylidene-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



m.p ≧ 250 °C
MS(m/z): 390 (SIMS)
NMR(DMSO-d_6) δppm: 7.2-7.7 (8H,m), 2.8-3.6 (12H,m), 2.26 (2H,quintet,J=7)

Example 15

1-Benzhydryl-4-[3-(1H-tetrazol-5-yl)propyl]-piperazine:



Benzhydrylpiperazine (10.62 g,42 mmol), 4-bromobutyronitrile (6.23 g, 42 mmol) and potassium carbonate(11.6 g, 84 mmol) were suspended in acetonitrile (200ml) and stirred overnight at 60 °C. The reaction solution was cooled and, thereafter, the inorganic matter

was filtered off and the acetonitrile was concentrated under vacuum to yield an oil of 4-(4-benzhydrylpiperazin-1-yl)butyronitrile (13.4 g, 99%).

MS (m/z) SI-MS,Pos: 319(M+H)

IR (Neat), cm^{-1}: 2250 (nitrile), 1490, 1445

Without further purification, 4-(4-benzhydrylpiperazin-1-yl)-butyronitrile was dissolved in DMF (150 ml) and ammonium chloride (6.74 g) and sodium azide (8.19 g) were added to the solution, followed by stirring at 90°C for 48 h. The reaction mixture was poured into water (300 ml), extracted with ethyl acetate (200 ml) and the extract was removed. Then, the aqueous layer was extracted twice with chloroform (200 ml). The chloroform layer was combined, dried with magnesium sulfate and concentrated under vacuum to reduce the volume of the solution to approximately 30 ml. Upon leaving the solution to stand, crystals precipitated and recovered by filtration to yield the titled compound (5.5 g).

Decomposition point: 218°C

MS (m/z) SI-MS,Pos: 363 (M+H)

Elemental analysis for $C_{21}H_{26}N_6$

	C	H	N
Cal'd	69.58	7.23	23.19
found	69.70	7.32	23.10

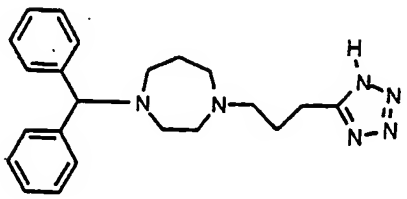
IR(nujol) cm^{-1}: 1405, 1310, 1192, 1087

^{1}H-NMR(DMSO-d_6) δppm: 50°C, 1.84 (2H,m), 2.2-3.7 (10H,m), 2.85 (2H,m), 4.27 (1H,s), 5.60 (2H,brs,H_2O), 7.0-7.4 (10H,m)

^{13}C-NMR(DMSO-d_6) δppm: 50°C, 156.07, 142.48, 128.16, 127.35, 126.54, 95.29, 74.83, 56.41, 52.42, 50.95, 23.80, 20.87

Example 16

1-Benzhydryl-4-[3-(1H-tetrazol-5-yl)propyl]-[1,4]diazepan:



The titled compound was synthesized via an intermediate nitrile form as in Example 1.

m.p. 172 - 175°C (from ethyl acetate)

MS (m/z) SI-MS : 377(M+H)

Elemental analysis for $C_{22}H_{28}N_6 \cdot 1/2H_2O$

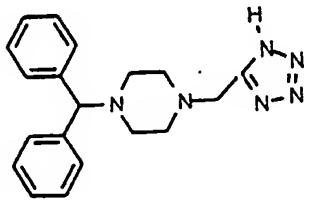
	C	H	N
Cal'd	68.54	7.58	21.80
found	68.60	7.45	21.85

IR(nujol) cm^{-1}: 1600, 1495, 1405, 1330, 1320

^{1}H-NMR(DMSO-d_6) δppm: 21.8°C, 1.81 (2H,m), 1.94 (2H,m), 2.4-2.7 (10H,m), 3.13 (2H,m), 4.71 (1H,s), 7.0-7.4 (10H,m)

Example 17

1-Benzhydryl-4-(1H-tetrazol-5-ylmethyl)piperazine:



m.p. 179 - 182°C (from ethyl acetate)

MS(m/z) SI-MS,Pos : 335(M+H)

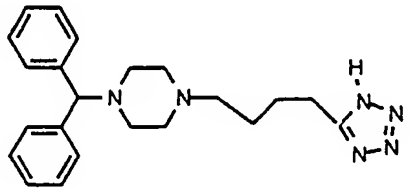
Elemental analysis for $C_{19}H_{22}N_6$

	C	H	N
Cal'd	68.24	6.63	25.13
found	68.10	6.54	25.10

IR(nujol) cm^{-1}: 2450, 1600, 1490, 1410, 1340, 1190, 1080, 1040, 970, 750, 710

Example 18

1-Benzhydryl-4-[4-(1H-tetrazol-5-yl)butyl]-piperazine



m.p. 67 - 68 °C

Elemental analysis for $C_{22}H_{28}N_6$

	c	H	N
Cal'd	70.18	7.50	22.30
found	70.10	7.40	22.35

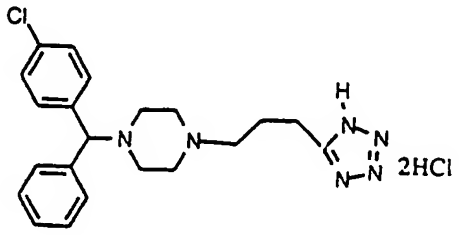
MS (m/z) SI-MS,Pos: 377(M+H)

IR(nujol) cm^{-1}: 1655, 1600, 1310, 1280, 1080, 970, 750, 710

^{1}H-NMR(DMSO-d_6) δppm: 1.56 (2H,m), 1.78 (2H,m), 2.49 (2H,m), 2.60 (8H,s), 2.95 (2H,t,J=7.2), 4.38 (1H,s), 7.28 (2H,t,J=7.0), 7.39 (2H,t,J=7.2), 7.52 (2H,d,J=7.6)

Example 19

1-[(4-Chlorophenyl)phenylmethyl]-4-[3-(1H-tetrazol-5-yl)propyl]piperazine dihydrochloride:



m.p. 198 - 203°C

MS(m/z) SI-MS, Pos: 397(M+H), 201, 166

Elemental analysis for $C_{21}H_{27}N_6Cl_3$

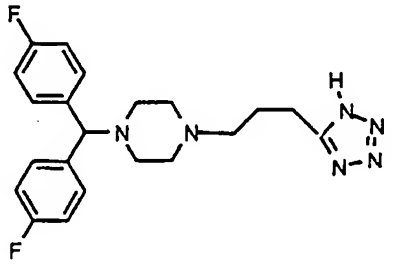
	C	H	N
Cal'd	53.68	5.79	17.89
found	53.65	5.90	17.91

IR(nujol) cm^{-1}: 1550, 1095, 1020, 760, 730

^{1}H-NMR(DMSO-d_6) σppm: 2.13 (2H,m), 2.98 (2H,t,J=7.0), 3.35 (4H,m), 3.63 (4H,m), 5.53 (1H,brs), 7.2-8.1 (9H,m)

Example 20

1-[Bis(4-fluorophenyl)methyl]-4-[3-(1H-tetrazol-5-yl)propyl]piperazine:



m.p. 170 - 172°C

MS (m/z) SI-MS: 399(M+H),203

Elemental analysis for $C_{21}H_{24}F_2N_6$

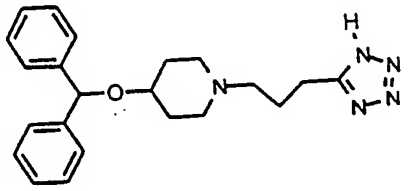
	C	H	N
Cal'd	63.30	6.07	21.09
Found	63.25	6.10	21.21

IR(nujol) cm^{-1}: 2100, 1600, 1500, 1400, 1300, 1225, 1090, 970, 870, 830, 725

^{1}H-NMR(DMSO-d_6) δppm: 1.85 (2H,m), 2.50 (10H,m), 2.86 (2H,t,J=7.3), 4.36 (1H,s), 7.12 (4H,t,J=8.9), 7.43 (4H,dd,J=8.2,5.9)

Example 21

4-Benzhydryloxy-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



The procedure of Example 20 was repeated to synthesize 4-(4-benzhydryloxypiperidin-1-yl)butyronitrile (2g, 5.3 mmol). This compound, as well as tributyltin azide (3.35 g, 10.6 mmol) were stirred in dimethoxyethane (DME) at 90°C for 48 h. Water was added to the reaction solution, followed by the addition of ethyl acetate (20 ml) and hexane (100 ml). The precipitating crystals were recovered by filtration and recrystallized from chloroform-ether to produce the titled compound (1.8 g) in a yield of 80%.

m.p. 216 - 217°C

MS (m/z) SI-MS, Pos: 378(M+H),167,133

Elemental analysis for $C_{22}H_{27}N_5O$

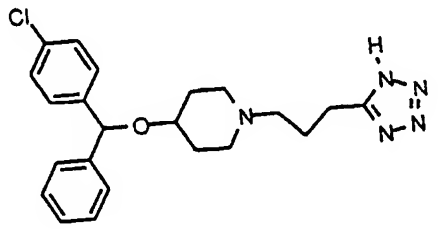
	C	H	N
Cal'd	70.00	7.21	18.55
Found	70.31	7.30	18.70

IR(nujol) cm^{-1} : 1500, 1400, 1300, 1260, 1220, 1110, 1060, 960, 745, 705

^{1}H-NMR (DMSO-d_6) δppm: 1.47 (2H,m), 1.96 (4H,m), 2.49 (2H,t,J=9.5), 2.68 (2H,t,J=6.7), 2.93 (4H,m), 5.73 (1H,s), 7.31 (2H,t,J=6.1Hz), 7.43 (8H,m)

Example 22

4-[(4-Chlorophenyl)phenylmethoxy]-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



The procedure of Example 1 was repeated to synthesize 4-{4-[(4-chlorophenyl)phenylmethoxy]piperidin-1-yl}butyronitrile (1.7 g, 4.6 mmol). This compound, as well as tributyltin azide (2.87 g, 9.2 mmol) were stirred in dimethoxyethane (DME) at 90°C for 48 h. Acetonitrile (10 ml) was added to the reaction solution, which was further stirred for 6 h at 90°C. Water was added to the reaction solution and the precipitating crystals were recovered by filtration. Upon recrystallization from chloroform-ether, the titled compound was obtained (1.3 g) in a yield of 69%.

m.p. 210 - 213°C

MS (m/z) SI-MS: 412(M+H), 201, 165

Elemental analysis for $C_{22}H_{26}ClN_5O$

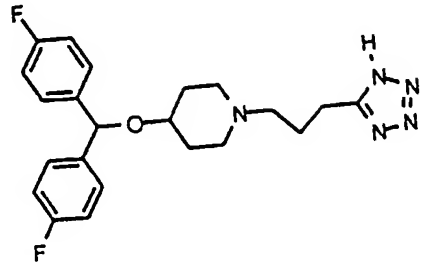
	C	H	N
Cal'd	64.15	6.36	17.00
Found	64.13	6.50	17.20

IR(nujol) cm^{-1}: 1495, 1400, 1300, 1090, 1055, 750, 710

^{1}H-NMR(DMSO-d_6) δppm: 1.75 (2H,m), 1.99 (4H,m), 2.61 (2H,m), 2.76 (2H,t,J=6.9), 2.93 (2H,t,J=7.3), 3.01 (2H,m), 5.73 (1H,s), 7.44 (9H,m)

Example 23

4[Bis(4-fluorophenyl)methoxy]-1-[3-(1H-tetrazol-5-yl)propyl]-piperidine:



Colorless powder

MS (m/z) SI-MS,Pos: 414(M+H), 203

Elemental analysis for $C_{22}H_{25}N_5O_2F_2$

	C	H	N
Cal'd	63.91	6.09	16.94
Found	63.81	6.20	16.90

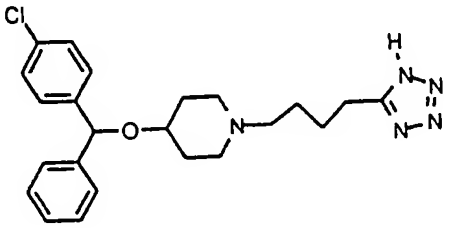
Hydrochloride

IR(nujol) cm^{-1}: 1500, 1400, 1260, 1120, 970, 830, 725

^1H-NMR(DMSO-d_6) δppm: 1.95 (2H,m), 2.16 (4H,m), 2.92 (8H,m), 3.52 (1H,m), 5.70 (1H,s), 7.15 (4H,m), 7.40 (4H,m)

Example 24

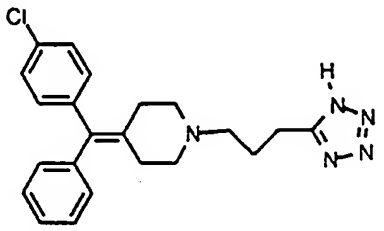
4-[(4-chlorophenyl)phenylmethoxy]-1-[4-(1H-tetrazol-5-yl)butyl]piperidine:



Colorless powder
FAB-MS (m/z) 425(M+H), 278, 202, 187
IR(nujol) cm^{-1}: 1500, 1400, 1260, 1120, 970, 830, 725
^{1}H-NMR(DMSO-d_6) δppm: 7.2-7.4 (9H,m), 5.62 (1H,s), 3.38 (1H,m), 2.84 (2H,t,J=6), 2.73 (2H,m), 2.37 (2H,t,J=6), 2.16 (2H,m), 1.4-2.0 (8H,m)

Example 25

4-[(4-Chlorophenyl)phenylmethylene]-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



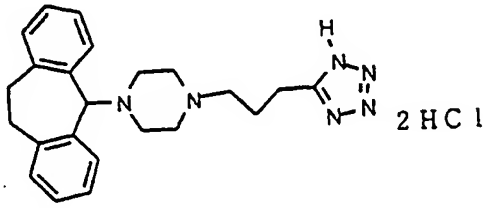
Colorless powder
MS (m/z) SI-MS,Pos: 393(M+H), 360, 296, 140
Elemental analysis for $C_{22}H_{23}N_5 \cdot 1.5H_2O$

	C	H	N
Cal'd	62.93	6.23	16.68
Found	63.15	5.90	17.09

IR (KBr) cm^{-1}: 3435, 2565, 1487, 1089, 1031, 964, 825, 763, 703, 509
^{1}H-NMR ($CDCl_3$) δppm: 7.32 (5H,m), 7.18 (4H,m), 3.20 (4H,m), 3.09 (4H,m), 2.87 (4H,m), 2.23 (2H,t,J=6)

Example 26

4-(Dibenzo[a,d]cycloheptan-5-yl)-1-[3-(1H-tetrazol-5-yl)propyl]piperazine dihydrochloride:



White amorphous

MS (m/z) SI-MS, Pos: 389(M+H), 194, 178, 114

Elemental analysis for $C_{24}H_3ON_6 2HCl \cdot H_2O$

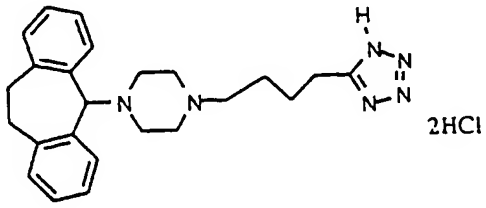
	C	H	N
Cal'd	57.62	6.30	17.53
Found	57.73	6.78	17.43

IR (KBr) cm^{-1}: 2997, 2725, 2584, 1635, 1560, 1442, 1419, 1076, 906, 630

^1H-NMR ($CDCl_3$) δppm: 7.35 (8H,m), 5.21 (1H,brs), 3.90 (2H,m), 3.37 (2H,brt), 3.27 (2H,t,J=6), 3.08 (4H,m), 2.31 (2H,m)

Example 27

4-(Dibenzo[a,d]cycloheptan-5-yl)-1-[4-(1H-tetrazol-5-yl)butyl]piperazine dihydrochloride:



White amorphous

MS (m/z) SI-MS, Pos: 403(M+H), 193

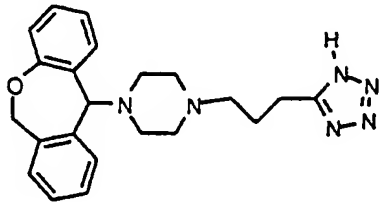
Elemental analysis for $C_{24}H_{30}ON_6 \cdot 2HCl \cdot 0.5H_2O$

	C	H	N
Cal'd	59.50	6.44	17.35
Found	59.41	7.03	16.91

IR (KBr) cm^{-1}: 2960, 1564, 1446, 1396, 1058, 773, 744
^{1}H-NMR($CDCl_3$) δppm: 7.38 (4H,m), 7.27 (4H,m), 5.21 (1H,brs), 3.91 (2H,m), 3.39 (2H,m), 3.22 (6H,m), 3.01 (4H,m), 1.87(4H,m)

Example 28

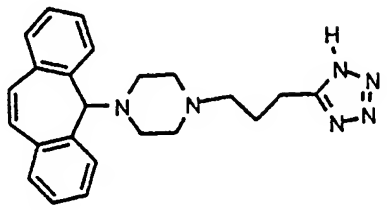
4-(6H-Dibenzo[b,e]-oxepin-11-yl)-1-[3-(1H-tetrazol-5-yl)propyl]piperazine:



White amorphous
MS (m/z) FAB-MS, Pos: 391(M+H), 195
IR(KBr) cm^{-1}: 3389, 2869, 1606, 1574, 1478, 1456, 1255, 1228, 1109, 1004, 761, 725, 638
^{1}H-NMR($CDCl_3$) δppm: 7.30 (4H,m), 7.15 (2H,t,J=7.5), 6.82 (2H,t,J=7.5), 6.72 (1H,d,J=11.5), 4.73 (1H,d,J=11.9), 4.03 (1H,s), 3.09 (2H,m), 2.73 (8H,m),
1.9-2.1 (2H,m)

Example 29

4-(Dibenzo[a,d]cyclohepten-5-yl)-1-[3-(1H-tetrazol-5-yl)propyl]piperidine:



White amorphous

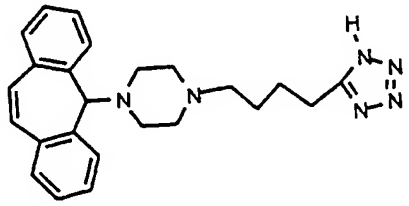
MS (m/z) FAB-MS, Pos: 387(M+H), 191

IR(KBr) cm^{-1}: 3392, 1654, 1436, 1402, 1276, 1103, 973, 796, 763, 730, 628, 493

^{1}H-NMR($CDCl_3$) δppm: 7.37 (8H,m), 6.94 (2H,s), 4.48 (1H,s), 3.18 (2H,t-like) 2.73 (2H,t-like), 2.69 (4H,m), 2.29 (4H,m), 1.95 (2H,m)

Example 30

4-(Dibenzo[a,d]cyclohepten-5-yl)-1-[4-(1H-tetrazol-5-yl)butyl]piperidine:



White amorphous

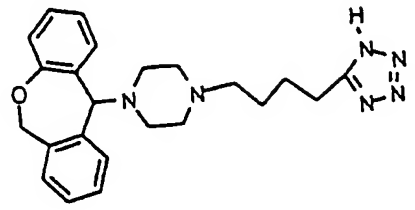
MS (m/z) FAB-MS, Pos: 401(M+H), 191

IR(KBr) cm^{-1}: 3045, 2871, 1635, 1436, 1402, 1247, 1103, 997, 798, 763, 730, 464

^{1}H-NMR($CDCl_3$) δppm: 7.31 (8H,m), 6.94 (2H,s), 4.40 (1H,s), 2.92 (2H,t,J=6.0), 2.64 (6H,m), 2.28 (4H,t,J=4.6), 1.78 (2H,m), 1.63 (2H,m)

Example 31

4-(6H-Dibenzo[b,e]oxepin-11-yl)-1-[4-(1H-tetrazol-5-yl)butyl]-piperazine:



White amorphous

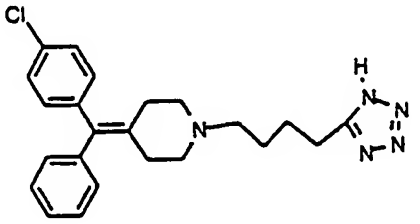
MS (m/z) FAB-MS,Pos: 405(M+H), 195

IR(KBr) cm^{-1}: 3485, 1487, 1446, 1255, 1228, 1109, 1004, 765

^{1}H-NMR($CDCl_3$) δppm: 7.29 (6H,m), 6.82 (2H,m), 6.69 (1H,d,J=11.5), 4.72 (1H,d,J=11.5), 4.00 (1H,s), 3.00 (2H,t,J=5.6), 2.5-2.9 (10H,m), 1,87 (2H,m), 1.71 (2H,m)

Example 32

4-[(4-Chlorophenyl)phenylmethylene]-1-[4-(1H-tetrazol-5-yl)butyl]piperidine:



White amorphous

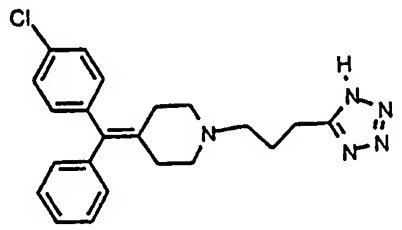
MS (m/z) FAB-MS,Pos: 408(M+H), 296

IR(KBr) cm^{-1}: 3438, 3099, 2763, 2650, 1487, 1442, 1398, 1087, 1014, 829, 763, 703

^{1}H-NMR($CDCl_3$) δppm: 7.26 (5H,m), 7.04 (4H,m), 3.00 (4H,t-like), 2.87 (2H,t-like), 2.70 (4H,t-like), 1.83 (4H,m)

Example 33

4-[(4-Chlorophenyl)phenylmethylene]-1-[3-(1H-tetrazol-5-yl)propyl)piperidine:



White amorphous

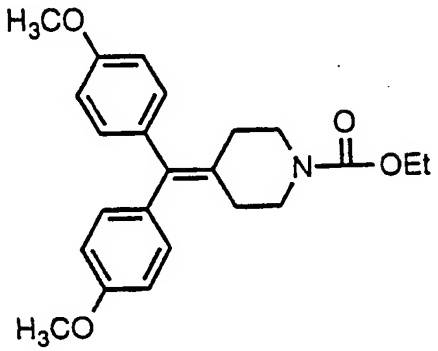
MS (m/z) FAB-MS, Pos: 393(M+H), 296

IR(KBr) cm^{-1}: 3436, 2565, 1487, 1089, 1031, 825, 763, 703

^{1}H-NMR($CDCl_3$) δppm: 7.32 (5H,m), 7.08 (4H,m), 3.15 (6H,m), 2.87 (2H,t-like), 2.30 (2H,m)

Example 34

4-[Bis(4-methoxyphenyl)methylene]-1-(ethoxycarbonyl)-piperidine:



A zinc powder (40.5 g, 0.62 mmol) was suspended in dry THF (500 ml) and titanium tetrachloride (34 ml, 0.30 mol) was added dropwise to the suspension at -10°C or below. The mixture was dried for 0.5 h and thereafter heated at 80°C for 1 h. The reaction solution was cooled again to 0°C and both 4,4'-dimethoxy-benzophenone (25 g, 0.103 mol) and 1-ethoxycarbonylpiperidone (18 g, 0.103 mol) as dissolved in THF (100 ml) were added. The reaction mixture was transferred to an oil bath, where it was heated under reflux at 80°C for 2 h. The reaction solution was cooled and poured into an aqueous solution of potassium carbonate. The THF layer was recovered and subjected to extraction with ethylacetate. The extracts were combined, dried and concentrated. The concentrate was subjected to silica gel chromatography and eluted with ethyl acetate-hexane (2:8) to yield the end product (34 g, 94%).

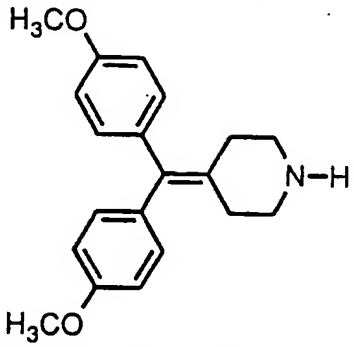
Oil

IR(nujol) cm^{-1}: 1735, 1605, 1578, 1490, 1390, 1130

$_1$H-NMR(DMSO-d_6) δppm: 7.01 (4H,d,J=9), 6.82 (4H,d,J=9), 4.15 (2H,q,J=7), 3.78 (6H,s), 3.49 (4H,m), 2.35 (4H,m), 1.25 (3H,t,J=7)

Example 35

4-[Bis(4-methoxyphenyl)methylene]piperidine:

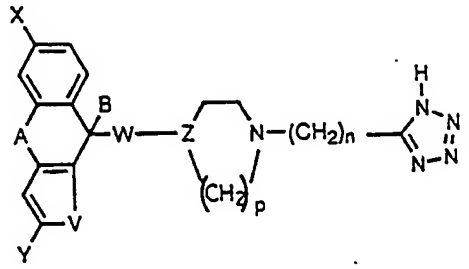


4-[Bis(4-methoxyphenyl)methylene]-1-(ethoxycarbonyl)piperidine (35 g) was dissolved in ethanol (300 ml) and potassium hydroxide (120 g) was added to the solution, which was then stirred over-night. Ethanol was concentrated, mixed with water (500 ml), subjected to extraction with chloroform (200 ml), dried and concentrated under vacuum. The residue was recrystallized from ethyl acetate-hexane to yield the end compound (20 g).

^{1}H-NMR ($CDCl_3$) δppm: 7.01 (4H,d,J=9), 6.82 (4H,d,J=9), 3.78 (6H,s), 2.90 (4H,m), 2.32 (4H,m)

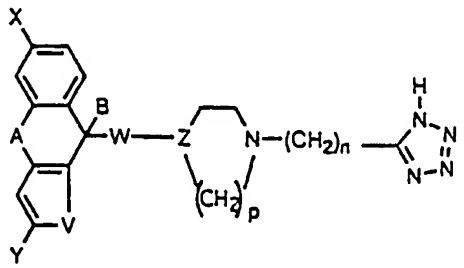
CLAIMS

1. A tetrazole derivative of the general formula (1):



(where A represents -CH=CH-, $-CH_2-CH_2-$, $-CH_2O-$, an oxygen atom or a sulfur atom or, in the case where A does not interconnect the adjacent aromatic rings, it represents two hydrogen atoms each bonded to the adjacent aromatic ring; V represents -CH=CH- or a sulfur atom; X and Y each independently represents an alkoxy group, a halogen atom or a hydrogen atom; (a) W represents a bond, Z represents a carbon atom or methine, and B either forms a bond together with Z or represents a hydroxyl group, or (b) W, Z and B represent a bond, a nitrogen atom and a hydrogen atom, respectively, or (c) W, Z and B represent an oxygen atom, methine and a hydrogen atom, respectively; p represents an integer of 2 or 3; and n represents an integer of 1 - 6) or a pharmacologically acceptable salt thereof.

2. An antihistamine, an antiallergic agent or an asthma treating agent that contain as an active ingredient a tetrazole derivative of the general formula (1):



(where A represents -CH=CH-, $-CH_2-CH_2-$, $-CH_2O-$, an oxygen atom or a sulfur atom or, in the case where A does not interconnect the adjacent aromatic rings, it represents

two hydrogen atoms each bonded to the adjacent aromatic ring, V represents -CH=CH- or a sulfur atom; X and Y each independently represents an alkoxy group, a halogen atom or a hydrogen atom; (a) W represents a bond, Z represents a carbon atom or methine, and B either forms a bond together with Z or represents a hydroxyl group, or (b) W, Z and B represent a bond, a nitrogen atom and a hydrogen atom, respectively, or (c) W, Z and B represent an oxygen atom, methine and a hydrogen atom, respectively; p represents an integer of 2 or 3; and n represents and integer of 1 - 6) or a pharmacologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/JP 94/01010

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/06 C07D405/14 C07D409/14 C07D257/04 C07D403/06
C07D405/12 A61K31/41 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 058 146 (UCB,S.A.) 18 August 1982 cited in the application *Document* ---	1,2
A	EP,A,0 468 884 (LABORATORIOS DEL DR. ESTEVE, S.A.) 29 January 1992 cited in the application & JP,A,4 234 387 (LABORATORIOS DEL DR. ESTEVE,S.A.) ---	1,2
A	EP,A,0 468 885 (LABORATORIOS DEL DR. ESTEVE,S.A.) 29 January 1992 cited in the application & JP,A,4 234 359 (LABORATORIOS DEL DR. ESTEVE,S.A.) --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 1994	20.09.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Luyten, H

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 94/01010

C.(Conunuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 9150, Derwent Publications Ltd., London, GB; AN 91-365831 & JP,A,3 246 287 (HOKURIKU PHARM KK) 22 February 1990 cited in the application see abstract -----	1,2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/JP 94/01010

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0058146	18-08-82	AT-T-	8140	15-07-84
		AU-B-	544066	16-05-85
		AU-A-	8023182	12-08-82
		CA-A-	1199918	28-01-86
		JP-C-	1463099	28-10-88
		JP-A-	57149282	14-09-82
		JP-B-	63011353	14-03-88
		SU-A-	1227113	23-04-86
		SU-A-	1310397	15-05-87
		SU-A-	1287749	30-01-87
		US-A-	4525358	25-06-85
EP-A-0468884	29-01-92	FR-A-	2665161	31-01-92
		AU-B-	638857	08-07-93
		AU-A-	8128091	30-01-92
		CN-A-	1058404	05-02-92
		JP-A-	4234387	24-08-92
		NZ-A-	239104	23-12-93
		US-A-	5182280	26-01-93
JP-A-4234387	24-08-92	FR-A-	2665161	31-01-92
		AU-B-	638857	08-07-93
		AU-A-	8128091	30-01-92
		CN-A-	1058404	05-02-92
		EP-A-	0468884	29-01-92
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